#9

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re PATENT APPLICATION of:

YANG ET AL.

Appln. No.: 09/398,897 Group Art Unit: 1647

Filed: September 20, 1999 Examiner: R. Hayes

For: STABLE NEURAL STEM CELLS

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DECLARATION PURSUANT TO 37 CFR 1.132

Assistant Commissioner
for Patents
Washington, DC 20231

Sir:

I, Karl K. Johe, Ph.D., declare as follows:

1. I am a co-inventor of the subject matter described and claimed in United States Patent Application 09/398,897, filed September 20, 1999, entitled "Stable Neural Stem Cells", which subject matter is disclosed and claimed in the above-referenced patent application.

2. This Declaration presents evidence to show that as of September 20, 1999, the filing date of the above-referenced patent application, persons of ordinary skill in the art knew what structurally constituted the c-myc constructs and the c-myc

DNA, as described and claimed in the above-referenced patent application.

3. The above-referenced patent application (page 4, line 21; and page 7, line 8) discloses the reference by Eilers et al. (Nature 340: 60-68, 1989) for the human c-myc DNA and the human estrogen receptor DNA, which is sufficient for those of ordinary skill in the art to make and use the invention disclosed in the above-referenced patent application.

4. The Eilers et al. article reports the original construction of the c-myc/estrogen receptor fusion gene which is used in the present application as a preferred example of a regulatable c-myc protein for obtaining stable neural precursor cell lines. In the article, Eilers et al. detail the identity of DNA elements used as well as their respective arrangement (see page 67, Fig. 1 legend and diagram). Specifically, it states (page 67, Fig. 1 legend, lines 2-3) "The human myc gene was used as a complementary DNA clone encompassing exons 2 and 3 of the genomic DNA[8]." (reference 8 therein: Stone, J. et al., Molec. Cell. Biol. 7: 1697-1709, 1987), which corresponded to amino acid residues 1-436 (diagram in Fig. 1, page 67). The human estrogen receptor was derived from a cDNA clone containing the amino acid residues 282-595 (reference 3 therein: Kumar, V. et al., EMBO J. 5: 2231-2236, 1986) (see page 67, Fig. 1 legend,

lines 7-8). The article further states that "The *mycer* gene was constructed by inserting a *Bam*H1 site at amino-acid position 436 into the human *myc* gene on plasmid pSP65-cmyc using the oligonucleotide 5'-GAACAGCTACGGGATCCTTGTGCGTAAGG-3'; subsequently, the *Bam*H1-*Eco*R1 fragment of plasmid HE-14 was inserted into a Bluescript vector (Stratagene) so that it became flanked with a *Hin*dIII site at its 3' terminus. The resulting *Bam*H1-*Hin*dIII fragment was inserted at the 3' end of the mutated *myc* gene into plasmid pSP65-cmyc. The chimaeric gene was inserted as an EcoR1 fragment into pMV-7." (see page 67, Fig. 1. legend, lines 16-24).

5. Furthermore, as of September 20, 1999, the publicly available GenBank DNA database contained the following complete cDNA sequences of the human c-myc gene and the human estrogen receptor gene.

LOCUS	HSMYC1 2121 bp mRNA PRI 17-FEB-1997
DEFINITION	Human mRNA encoding the c-myc oncogene.
ACCESSION	V00568
VERSION	V00568.1 GI:34815
KEYWORDS	complementary DNA; oncogene.
SOURCE	human.
ORGANISM	Homo sapiens Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
REFERENCE	1 (bases 1 to 2121)
AUTHORS	Watt,R., Stanton,L.W., Marcu,K.B., Gallo,R.C., Croce,C.M. and Rovera,G.
TITLE	Nucleotide sequence of cloned cDNA of human c-myc oncogene
JOURNAL	Nature 303 (5919), 725-728 (1983)
MEDLINE	83219310

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REFERENCE   2  (bases 833 to 834)
  AUTHORS   Watt,R.
  TITLE     Direct Submission
  JOURNAL   Submitted (18-JUL-1983)
COMMENT     Data kindly reviewed (18-JUL-1983) by Watt R.
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REFERENCE   1  (bases 1 to 6450)
  AUTHORS   Greene GL, Gilna P, Waterfield M, Baker A, Hort Y and Shine J.
  TITLE     Sequence and expression of human estrogen receptor complementary
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  JOURNAL   Science 231 (4742), 1150-1154 (1986)
  MEDLINE   86122927
   PUBMED   3753802
REFERENCE   2  (bases 1 to 6450)
  AUTHORS   Green,S., Walter,P., Kumar,V., Krust,A., Bornert,J.M., Argos,P.
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  TITLE     Human oestrogen receptor cDNA: sequence, expression and homology
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REFERENCE   3  (bases 1 to 6450)
  AUTHORS   Menasce LP, White GR, Harrison CJ and Boyle JM.
  TITLE     Localization of the estrogen receptor locus (ESR) to chromosome
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  JOURNAL   Genomics 17 (1), 263-265 (1993)
  MEDLINE   94010905
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REFERENCE   4  (bases 1 to 6450)
  AUTHORS   Pink JJ, Wu SQ, Wolf DM, Bilimoria MM and Jordan VC.
  TITLE     A novel 80 kDa human estrogen receptor containing a duplication
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            exons 6 and 7
  JOURNAL   Nucleic Acids Res. 24 (5), 962-969 (1996)
  MEDLINE   96174665
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COMMENT     PROVISIONAL REFSEQ: This record has not yet been subject to final
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5401 taaggtgttc tcaccttgaa atcttataca ctgaaatggc cattgattta ggccactggc
5461 ttagagtact ccttcccctg catgacactg attacaaata ctttcctatt catactttcc
5521 aattatgaga tggactgtgg gtactgggag tgatcactaa caccatagta atgtctaata
5581 ttcacaggca gatctgcttg gggaagctag ttatgtgaaa ggcaaataaa gtcatacagt

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5641 agctcaaaag gcaaccataa ttctctttgg tgcaagtctt gggagcgtga tctagattac
5701 actgcaccat tcccaagtta atcccctgaa aacttactct caactggagc aaatgaactt
5761 tggtcccaaa tatccatctt ttcagtagcg ttaattatgc tctgtttcca actgcatttc
5821 ctttccaatt gaattaaagt gtggcctcgt ttttagtcat ttaaaattgt tttctaagta
5881 attgctgcct ctattatggc acttcaattt tgcactgtct tttgagattc aagaaaaatt
5941 tctattcatt tttttgcatc caattgtgcc tgaactttta aaatatgtaa atgctgccat
6001 gttccaaacc catcgtcagt gtgtgtgttt agagctgtgc accctagaaa caacatactt
6061 gtcccatgag caggtgcctg agacacagac ccctttgcat tcacagagag gtcattggtt
6121 atagagactt gaattaataa gtgacattat gccagtttct gttctctcac aggtgataaa
6181 caatgctttt tgtgcactac atactcttca gtgtagagct cttgttttat gggaaaaggc
6241 tcaaatgcca aattgtgttt gatggattaa tatgcccttt tgccgatgca tactattact
6301 gatgtgactc ggttttgtcg cagctttgct ttgtttaatg aaacacactt gtaaacctct
6361 tttgcacttt gaaaaagaat ccagcgggat gctcgagcac ctgtaaacaa ttttctcaac
6421 ctatttgatg ttcaaataaa gaattaaact
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6. Copies of the above-cited Green et al., Kumar et al., Stone et al. and Watt et al. references were submitted with the Information Disclosure Statement hand delivered to the Examiner on November 14, 2001.

7. In addition, at least 10 scientific articles and patents submitted with the Information Disclosure Statement, filed December 29, 1999, in the above-referenced patent application relate to the c-myc constructs and the c-myc gene.

For example, Reichmann, E. et al., Cell 71: 1103-1116, 1992 (Page 1104, Figure 1) shows a 'cartoon' of the c-mycER fusion gene as well as other fusion constructs as used in a retroviral vector. The authors specifically cite Eilers et al., 1989, as the source of the c-mycER construct (see page 1104, left column; page 1113, right column, under "Retroviral Infection").

Selvakumaran, M. et al., Blood 81: 2257-2262, 1993, used the same c-mycer fusion DNA as in the above-referenced patent

application and referenced the same source, i.e., Eilers et al., as the origin and structure of the gene (see page 2257, right column, under "Retroviral infections").

Nakafuku, M. et al., J. Neurosci. Res. 41: 153-168, 1995, utilized the same c-mycer construct as the above-referenced patent application and also cited Eilers et al., 1989, as the reference for its structure (see page 156., Fig. 1, legend and diagram A).

Finally, U.S. Patent 5,580,777 (Bernard et al.), cited by the Examiner in the claim rejections under 35 USC 103, referred to the c-myc constructs and the c-myc gene by references to numerous scientific articles (see, for example, column 1, lines 62-64; column 4, lines 54-61).

8. Therefore, as of September 20, 1999, the filing date of the above-referenced patent application, persons of ordinary skill in the art knew what structurally constituted the c-myc constructs and the c-myc DNA, as described and claimed in the above-referenced patent application.

9. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or

imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: Nov. 14, 2001 By: Karl K. Johe, Ph.D.